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WO 2004/067002 A3

(54) Title: **SELECTIVE mGlu5 ANTAGONISTS FOR TREATMENT OF NEUROMUSCULAR DYSFUNCTION OF THE LOWER URINARY TRACT**

(57) Abstract: Antagonists that are selective for the metabotropic mGlu5 receptor over at least one of the metabotropic mGlu receptor, mGlu2 receptor and mGlu3 receptor, and preferably selective over all three thereof, are useful for the preparation of medicaments for the treatment of neuromuscular dysfunction of the lower urinary tract in mammals. A wide variety of suitable compounds is described. The medicament may contain the selective mGlu5 antagonist as the sole active agent, or may also contain one or more additional therapeutic agents for the treatment of neuromuscular dysfunction of the lower urinary tract in mammals. Also provided are methods of identifying selective mGlu5 antagonists that are useful for treating neuromuscular dysfunction of the lower urinary tract in mammals.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/000951

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K31/44	A61K31/4965	A61K31/497	A61K31/427	A61P13/02
	A61P13/10	A61P25/02			

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/002983 A (EURO CELTIQUE SA ; KYLE DONALD J (US); SUN QUN (US); ZHANG CHONGWU (US) 8 January 2004 (2004-01-08) abstract	19-23
P,Y	claims 132-146	1-5
P,X	----- WO 03/066595 A (EURO CELTIQUE SA ; KYLE DONALD J (US); SUN QUN (US))	19-23
P,Y	14 August 2003 (2003-08-14) page 91, lines 15,16,23-26	1-5
P,X	----- WO 03/093236 A (EURO CELTIQUE SA ; KYLE DONALD J (US); SUN QUN (US); YANG JI (US); ZHO) 13 November 2003 (2003-11-13)	19-23
P,Y	page 131, paragraph 2 claims 71-77	1-5
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "V" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

16 June 2004

Date of mailing of the international search report

01.10.2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	TANAKA HIROSHI ET AL: "Effects of a selective metabotropic glutamate receptor agonist on the micturition reflex pathway in urethane-anesthetized rats." NEUROUROLOGY AND URODYNAMICS, vol. 22, no. 6, 2003, pages 611-616, XP009032144 ISSN: 0733-2467 abstract -----	19-23
X	WO 02/46166 A (HOFFMANN LA ROCHE) 13 June 2002 (2002-06-13)	19-23
Y	page 4, line 5 page 17, lines 15,16 claims -----	1-5
X	WO 02/094795 A (HOFFMANN LA ROCHE) 28 November 2002 (2002-11-28)	19-23
Y	page 2, lines 30,31 page 11, lines 22,23 claims -----	1-5
X	WO 02/092086 A (HOFFMANN LA ROCHE) 21 November 2002 (2002-11-21)	19-23
Y	page 4, lines 7,8 page 8, lines 27,28 claims -----	1-5
Y	WO 99/02497 A (NOVARTIS ERFIND VERWALT GMBH ; HECKENDÖRN ROLAND (CH) ; AUBERSON YVES () 21 January 1999 (1999-01-21) the whole document -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/000951

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely.
2. Claims Nos.: 19-21 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.

1-5, 19-23

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 19-21

Present claims 19-21 relate to a compound defined by reference to a desirable characteristic or property, namely its binding affinity to the mGlu5 receptor. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally defined in the description/claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5, 19-23

Use of a compound of generic formula (I) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

2. claims: 6,19-23

Use of a compound of generic formula (II-A) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

3. claims: 7-9, 19-23

Use of a compound of generic formulae (II-B)/(II-C) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

4. claims: 11,12,19-23

Use of a compound of generic formula (III) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

5. claims: 13,19-23

Use of a compound of generic formula (IV) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

6. claims: 14-16,19-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a compound of generic formula (V-A) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

7. claims: 17-23

Use of a compound of generic formula (V-B) for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract. A method for identifying a compound useful for treating neuromuscular dysfunction of the lower urinary tract, the method comprising the steps as defined in claim 22.

INTERNATIONAL SEARCH REPORT

Information on patent family members.

International Application No.
PCT/EP2004/000951

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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Form PCT/ISA/210 (patent family annex) (January 2004)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/000951

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902497	A	ZA 9806137 A	22-01-1999

Form PCT/ISA/210 (patent family annex) (January 2004)